FATAL ACETONÆMIA FOLLOWING AN OPERATION FOR ACUTE APPENDICITIS.[1]

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THE object of this communication is to report and place on record the history of a case of acute perforative appendicitis, which was apparently progressing favorably after operation, in which death probably resulted from an acute autointoxication of the type seen frequently in diabetics and described under the term acetonæmia. The condition is in the writer's experience absolutely unique, and he has been unable thus far to find any record in literature of its occurrence as a fatal surgical complication in non-diabetic cases.

S. S., aged twelve years, a school-boy, was admitted to the Roosevelt Hospital on April 29, 1901. There was nothing in the family history nor in the previous history of the patient which could have any bearing upon the pathological condition which is to be described. Previous to this illness he presented every evidence of the most robust health.

Two days before his admission, after a long and rather fatiguing military drill at his school, he was suddenly seized with an acute abdominal pain, which was more or less general at first, and was accompanied by nausea and vomiting. Later the pain became more severe, and was referred to the right inguinal region. There was a slight elevation of temperature and an increase in the pulse-rate. He was seen by Dr. Edson, his family physician, early in the evening, and on examination he found tenderness

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and muscular rigidity in the right lower quadrant of the abdomen. Appropriate treatment was prescribed, including an ice-bag to the inguinal region. The following day there was a very considerable improvement in all the symptoms; the temperature had fallen to 99.8° F., pulse to 90, and there was no pain.

He passed a comfortable day, but during the following night the pain returned, and on the morning of his admission to the hospital, as the temperature was 101° F., pulse 110, leucocytes 17,000, an immediate operation was advised. After the usual preparation, under chloroform anæsthesia, an incision was made over the region of the appendix and the abdominal cavity opened by the intermuscular method. Examination revealed the presence of a tumor composed of intestine, omentum, and the inflamed appendix glued together with plastic exudate, and situated in the iliac fossa near the anterior superior spinous process. After walling off the intestines with gauze pads, the adhesions were separated, and a perforated gangrenous appendix found in a small abscess cavity which contained about two drachms of foul-smelling pus. The appendix was removed, the cavity disinfected, two cigarette drains introduced, and the wound partly closed.

Duration of anæsthesia about twenty-five minutes.

After his return to his room, the temperature was found to be 103° F., pulse 120, and of good quality. As his general condition at that time seemed satisfactory, no stimulation was ordered. Considerable pain followed his recovery from the anæsthetic, which was relieved by one-eighth grain of morphine. There was no vomiting, and he was able to take and retain water by the mouth four hours after the operation. During the night he became restless and complained of more pain, but was again quieted by a small dose of codeine. The following morning he seemed bright, the temperature had fallen to 101° F. and the pulse to 88; he took and retained fluid food; later in the day there was a still further drop in the temperature. He complained of some distention; an enema was given, which resulted in a fairly large yellow movement.

The second night after operation was a comfortable one; his distention was relieved, gas passed freely by the rectum, and he slept about six hours. The following morning his temperature had fallen to normal, his pulse to 76; he seemed cheerful and happy and expressed himself as free from pain and hungry.

The wound was dressed, and was found to be in a satisfactory condition. The abdomen was flat; there was no rigidity, and only slight tenderness in the wound area. Calomel and salts were administered; the bowels moved again, and much gas was expelled.

During the entire day his temperature remained normal and his pulse never rose above 80. He slept most of the afternoon and made no complaint. The urine, which before operation had been normal, to-day showed a slight trace of albumen and a few finely granular and hyaline casts; no sugar, pus, or blood.

The following night he slept quietly until shortly after midnight, when he suddenly awakened and, without any apparent cause, uttered a piercing shriek, which was so agonizing and expressive of terror that it not only greatly alarmed his nurse, but also his mother, who was sleeping in an adjoining room. He continued to scream for several seconds, looked wildly about, and apparently failed to recognize those around him. A few moments later he again fell asleep and rested quietly until the morning. The symptoms were at first attributed to a bad dream or nightmare. The following morning he was distinctly somnolent, and when aroused would cry out and appear for a moment very much frightened, but would be easily soothed by his mother, after which he would again fall into a quiet sleep. His temperature was 98.5° F., pulse 74; the abdomen was soft; there was no distention; the secretion of urine was free and of the same character as on the preceding day. He was seen by the writer at about eleven o'clock in the morning. He was then sleeping soundly, and appeared in every way normal. On waking him, he again uttered an agonizing cry and looked the picture of abject terror. His eyes wandered from one person to another without the slightest sign of recognition. He continued to scream with such vehemence that his cries were heard all over the building. All efforts to soothe him seemed unavailing; his terror was painful to witness, and the whole picture suggested unspeakable fright and the most acute mental suffering. These paroxysms would last from a few seconds to two or three minutes, and would be succeeded by a comparatively long interval of rest, during which he would apparently be sleeping quietly.

The pupils were symmetrical and reacted to light and accommodation. There was no evidence of cranial nerve palsy or

irritation. There was no impairment of sensation or motion in any part of the body; the reflexes were apparently unaffected. His temperature and pulse remained normal, and there was nothing to indicate any gastro-intestinal irritation, pulmonary or cardiac disturbance. I immediately called my colleague, Dr. Blake, in consultation, and, after a thorough examination, he agreed with me that the wound conditions were satisfactory, and that there was no evidence of sepsis. He was unable, however, to offer any explanation of the mental symptoms, and we both agreed that the opinion of an expert neurologist should be obtained as soon as possible. As the parents urged us to call upon any one who could be of service to us, a consultation was quickly called, at which Dr. Edson, the family physician, Dr. Blake, Dr. Pearce Bailey, and Dr. George L. Peabody were present. After carefully reviewing the history of the case from the beginning, and repeating the previous examinations, during which the child passed through several of the screaming paroxysms, the consensus of opinion as expressed was that the patient presented evidences of extreme cerebral irritation, the cause or causes of which could not at that time be discovered, as none of the gentlemen present had ever seen or heard of a similar case.

During or shortly after the consultation the writer noticed a peculiar sweetish, ethereal odor of the breath, which was verified by each one present. The nurse stated, in answer to inquiries, that she had noticed that peculiar odor ever since she came on duty at seven o'clock in the morning. The opinion was expressed that the odor was in all probability that of acetone, and indicated a condition of acetonæmia which might be a causative factor in the production of the symptoms. As none of those present at the consultation had ever observed symptoms due to acetonæmia in conditions other than diabetes, and as the symptoms of acetonæmia in diabetes were usually those of a rapidly deepening coma, rather than delirium and cerebral irritability, no definite conclusions could be arrived at until more complete examination of the urine or blood could be made, and further observations of the symptoms and progress of the case. Meanwhile the symptoms were increasing in severity, the paroxysms occurring more frequently, the character of the delirium becoming more distressing, and the intervening sleep deeper and more resembling coma. At 6 P.M. the temperature was still normal; the pulse during sleep 80, but

weaker; physical signs unchanged. An hour later the patient was seen in consultation by Dr. Evan Evans, who expressed very positively the belief that the symptoms were due to an acute auto-intoxication which is associated with the presence of acetone and diacetic acid in the blood. He gave an extremely grave prognosis, predicting death within twenty-four hours unless the symptoms were speedily relieved by free catharsis, diuresis, and the intravenous injection of a solution of chemically pure bicarbonate of sodium. He volunteered to make a thorough analysis of the urine and blood, which he did immediately at the pathological laboratory of the College of Physicians and Surgeons.

The result of this analysis showed large quantities of both acetone and diacetic acid in the urine and blood.

The subsequent history of the case is as follows:

At 8 P.M. about 400 cubic centimetres of blood were withdrawn from the median cephalic vein of the left arm and sent to the laboratory for examination, after which he was given an infusion of about 1000 cubic centimetres of normal salt solution, to the last of which about fifteen grammes of chemically pure bicarbonate of sodium were added. The stomach was next washed and a large dose of calomel and Epsom salts introduced through the tube. After an hour's rest he was given a prolonged hot saline irrigation of the rectum by means of a Kemp's tube. An hour later another dose of Epsom salts was administered with a stomach-tube, followed by a high enema of turpentine, glycerin, and soap-suds. As there had been no spontaneous urination for several hours, he was catheterized, and a moderate quantity of urine withdrawn having a very strong odor of acetone.

During this time the character of the symptoms underwent a change. The paroxysms of screaming were of shorter duration, and occurred less frequently; the intervening sleep was more profound, and he was less easily awakened by treatment; the pupils seemed more dilated; there was no change in the temperature, although the pulse increased somewhat in frequency and was evidently growing weaker. The circulation in the extremities was slower; the face seemed slightly cyanosed; the eyes expressionless. Shortly after midnight, as the bowels had not moved, and as it was thought that the intra-abdominal cigarette drains might be causing mechanical obstruction, the wound was dressed and the drains removed. It was then observed that the abdomen

was somewhat distended. An hour later, as his condition seemed unchanged, he was given two ounces of castor oil and two minims of croton oil through the stomach-tube, and the hot saline rectal irrigation repeated. About 3 A.M., as no movement had occurred, he was given another high enema of turpentine and glycerin without result.

Between four and five his condition began to change for the worse; the respiration became shallow and more rapid, the pulse was weaker, and the temperature rose rapidly to 103° F.; the paroxysms of acute delirium ceased, and he fell into a condition of progressively deepening coma. As there had been no movement from the bowels, as a last resort, early in the morning the cæcum was opened in the wound and the bowel freely irrigated, but without producing any change in the symptoms, which steadily progressed until eleven in the morning, when he died.

In the absence of an autopsy, which, under the circumstances, it was impossible to obtain, the only method of correctly interpreting these extraordinary symptoms and arriving at a correct diagnosis is by the method of exclusion. Briefly stated, we have to do in this case with a localized septic focus in the abdominal cavity, well protected by nature, and thoroughly removed by operation. Following its removal, there was a rapid subsidence of all septic manifestation, evidenced by a progressive fall to the normal of the pulse and temperature, the disappearance of all pain, rigidity, and distention, free evacuation of the bowels, and a general and progressive improvement in the patient's appearance, behavior, and feelings. In the midst of this improvement, and unaccompanied by any evidence of either local or general sepsis, there suddenly occurred acute delirium, frightful hallucinations, a failure to appreciate his surroundings or recognize those about him, somnolence, coma, and death within thirty-two hours from the first untoward symptom.

The irritant which produced this extraordinary and rapidly fatal cerebral disturbance must have been a very powerful one, or one which was developed in large quantities during a very short period of time. Of the various causes which might

give rise to such a train of symptoms, we must consider, first, traumatism; second, septic infection, local or general; third, the toxic action of drugs, and, fourth, auto-intoxication.

Traumatism can be absolutely excluded by the history. Of the septic processes which might act as a causative agent, we must consider acute meningitis or cerebritis, from middle ear suppuration, frontal sinus, or ethmoidal disease; epidemic cerebrospinal meningitis; or a metastatic process from the abdominal focus. The first three can be absolutely excluded by the history and result of local examinations, as well as by the fact of the acuteness of the onset, rapidity of progress, and early termination. These facts, together with the complete absence of fever or general illness, would serve also to exclude epidemic cerebrospinal meningitis. Septic meningitis, in the writer's opinion, can be absolutely excluded by the absence of prodromal headache, restlessness, intolerance of light and sound, from the extremely sudden development of the gravest mental disturbances without the slightest premonitory sign, from the absence of fever and the presence throughout of a slow, calm, even pulse, which remained at a point generally below 80 until a few hours before his death.

It is impossible to conceive of a septic meningitis of such virulence, that it ran its course from the first sign to a fatal coma in thirty-two hours, to exist without fever. Moreover, a metastasis of such virulence would not be likely to occur after the complete removal of the original focus and after three days of rapid improvement in all the symptoms. That we may have structural changes in the meninges accompanied by exudate, as in the other serous membranes of the body, due wholly to an intense toxæmia from some remote septic focus, will not be questioned. In fact, one of the consultants suggested this as a possible explanation of the symptom in this case. The writer believes, however, that this can be excluded, from the fact that the symptoms did not appear during the stage of the disease when the toxæmia was necessarily greatest, before the removal of the septic focus, but did appear after

the disappearance of all indications of toxæmia, as evidenced by a disappearance of the local inflammatory conditions, and a return to the normal of the temperature and pulse. Moreover, one would not expect a toxæmia of that virulence to manifest itself by cerebral symptoms alone, with a complete absence of the other ordinary indications of such a condition.

The toxic action of drugs can be positively excluded in this case, as only one-eighth of a grain of morphine, a very small amount of codeine, Epsom salts, and calomel had been administered.

Of the auto-intoxications, three varieties must be considered,—ptomaine poisoning, uræmia, and acetonæmia.

In ptomaine poisoning the symptoms are due to the local and general effect of toxic substances which are generated in the gastro-intestinal tract by various fermentative and putrefactive processes. The symptoms are similar to those produced by some powerful and poisonous alkaloid. There is acute prostration with rapid, feeble pulse; cold perspiration and subnormal temperature, accompanied often by severe vomiting and purging. The symptoms appear suddenly, the progress of the disease is rapid, in the fatal cases death occurring often in a few hours. The absence of any symptoms of prostration or gastro-intestinal irritation, and the fact that the diet had been limited to milk, broths, and rice would serve to exclude this disease.

Uræmia can be excluded by the absence of any evidence of previous disease of the kidneys, and by the fact that up to within a few hours of death a full amount of urine was secreted containing a normal output of solids. Moreover, there was nothing whatever in the clinical picture to suggest uræmia.

If we are justified in excluding the above conditions, it is the writer's opinion that we must assume that the cause of death in this instance was the occurrence of that form of auto-intoxication described as acetonæmia.

That the term acetonæmia is a misleading one will be

evident from the following brief *résumé* of the facts bearing upon our present knowledge of this condition.

Acetone is a colorless, limpid fluid, of a sweetish, ethereal odor, and has been known chemically for many years.

It was first discovered as a pathological constituent of the urine by Pettus in 1857, who observed it in a case of diabetic coma. Kaulich afterwards found it constantly present in varying quantities in all stages of the disease. Kussmaul in 1874 described the symptoms of diabetic coma, but threw some doubt on the toxic action of acetone as a causative factor; and, later, Gerhardt and others demonstrated the constant association of diacetic acid and B. oxybutyric acid with acetone in the blood and urine. Without going further into the history of the subject, it may be stated that, under certain conditions of the body metabolism, the most important of which, according to Herter, is an increased destruction of proteid matter, acetone appears in variable quantities in the blood and urine, and if present in large amount is associated with the presence of diacetic and B. oxybutyric acids, and possibly some other volatile fatty acids. This is the condition usually spoken of as acetonæmia, but it is better described by the term "acid intoxication," or excessive "acidosis."

This condition is often associated with grave cerebral disturbances, of which delirium and coma are prominent symptoms, and, if the intoxication is of greater intensity, death speedily results. At first the toxic agent was thought to be the acetone, but this was afterwards proved by animal experiments to be harmless. Later, the diacetic and B. oxybutyric acids were held responsible for the symptoms; but later investigation has shown that the symptoms, to a large extent at least, depend upon an entirely different cause.

It has been recently demonstrated that the presence of these three substances in the blood results in a marked diminution in its normal alkalinity, upon which depends its ability to absorb carbon dioxide from the tissues, and that the symptom complex in this condition is due rather to a rapid carbon dioxide poisoning of the tissues than to the toxic effect of any

or all of these substances, although it is held by some authorities that the oxybutyric acid and the probably associated volatile fatty acids are in themselves to some extent toxic.

The three characteristic symptoms of this condition are, a well-marked sweetish, ethereal odor of the breath, delirium, and a rapidly fatal coma. In the great majority of instances the stage of cerebral excitation is brief and often overlooked, the only symptom appearing to be a progressingly deepening coma.

Other symptoms are occasionally observed, among which may be mentioned the "air hunger" described by Kussmaul, and evidenced by increased rapidity and depth of respirations, with a bright red color of the mucous membranes and the skin, due to the presence of aërated blood in the veins from the inability to absorb carbon dioxide from the tissues. R. T. Williamson, in the "Encyclopædia Medica," describes an alcoholic type in which the stage of cerebral excitation is most marked, the patients becoming wildly delirious, and exhibiting evidences of fright strongly resembling delirium tremens. This type of this disease is perhaps more common in children, and has been described in the *Traité des Maladies de l'Enfants* by Graucher, Comby, and Marfan in the following manner: "In other cases the child is seized by violent agitation, with groaning and unintelligible cries, incoördinate movements, and delirium, the coma manifesting itself only after the period of excitation has passed. The temperature is often subnormal."

Regarding the odor of the breath, the writer continues: "Many cases are signalized by a peculiar odor of the breath; a pungent or vionaceous odor or the odor of acetone itself, sometimes comparable to that of a pippin apple, sometimes to that of chloroform. It may be quite faint, appreciable only on leaning over the bed near the patient's mouth, or very marked, filling the whole room."

While this condition of acid intoxication was formerly thought to occur to a fatal degree only in diabetes, a sufficient number of cases have been reported to conclusively demon-

strate that it can occur independently of that disease. Clinical and experimental researches have shown that it may occur in infectious fevers and general sepsis; in intestinal fermentation and putrefaction; in pregnancy with the presence of a dead fœtus, in brain lesions, in tabes, paresis, and melancholia, as a result of general anæsthesia from both ether and chloroform; after extirpation of the pancreas in animals; and under conditions of a changed diet, especially the complete elimination of carbohydrates from the food, and in starvation.

Seeking to establish the cause or causes of death in the so-called cases of "chronic chloroform intoxication" described by Casper, König, Volkmann, and others, Kast and Mester (*Zeitschrift für klinische Medicin,* Band xviii, p. 469), in 1891 undertook a series of observations upon the urine of patients, after anæsthesia by chloroform, and found, among other substances indicating increased destruction of proteid matter, a condition of hyperacidity, the cause of which was not at that time determined. Later, Ernst Becker (*Deutsche medicinische Wochenschrift,* 1894, Band xviii, p. 469, *Virchow's Archives,* Vol. cxl, p. 1), after observation of a large number of cases in which general anæsthesia was immediately followed by symptoms of acute acetonæmia in diabetes, systematically examined the urine of several hundred healthy individuals, before and after the administration of the various anæsthetics, with the result that in over sixty per cent. of his cases general anæsthesia was followed by a pathological amount of acetone in the urine; that the highest percentage occurred after chloroform narcosis, and that it was more frequently observed in children than adults. He reports one case in which the classical symptoms of acidosis, hallucinations, cries, stupor, coma, air hunger, cold extremities, Cheyne-Stokes respiration, etc., followed general anæsthesia, associated with marked acetonuria. The symptoms were alarming and lasted nineteen hours. The life of the patient was saved only by the persistent employment of artificial respiration and active stimulation. The urine was free from acetone before the anæsthetic, and at no time contained albumen or sugar.

In a series of observations undertaken at the Roosevelt Hospital by Dr. J. H. Blue, at the suggestion of the writer, the presence in the urine of a pathological amount of acetone occurred in seven out of thirty-three cases following anæsthesia. In five of these chloroform had been used, and in two ether. None of the cases were diabetic, and in none was there a reaction for acetone before the administration of the anæsthetic. In all the acetone appeared on the day following the operation. In two it was found on the second and third days, in the remaining five on the second. In six of the cases there were no symptoms which could be attributed to acidosis; in the seventh death occurred thirty-six hours after a gastro-enterostomy for carcinoma, with rather indefinite symptoms of so-called secondary shock.

While these observations by no means establish the fact that a condition of true acid intoxication was present in seven of our thirty-three cases, as there was no proof that the urine contained either diacetic or B. oxybutyric acid, they show at least that there was in these cases an increased destruction of proteid matter, a condition which may be regarded as the first step in a pathological process which, if continued, would probably lead to a condition of acidosis sufficient to give rise to symptoms.

I think most surgeons have had the experience of seeing certain patients die on the second or third day after comparatively simple operations, exhibiting indefinite toxæmic symptoms which occur rather too early to be attributed to sepsis and rather too late to be accounted for by shock—a condition which is often described by the indefinite and meaningless phrase "secondary shock." It may be that later investigation will show this condition of acid intoxication to be a factor in some of these cases.

In conclusion, the writer desires to say that it is his intention to continue these investigations, and if any facts are obtained bearing upon surgical acetonæmia which are worthy of record, to present them at a subsequent meeting of the

Association. This communication he hopes will simply be regarded as a preliminary report.

ADDENDUM.

Test for Acetone.—Place about twenty cubic centimetres of the urine in a small glass retort, heat over an alcohol flame, and condense vapor in a cold test-tube; then add small amount of potassium hydrate to render reaction alkaline, after which add four or five drops of Gram's solution of iodopotassic iodide, and heat gently. If acetone is present, a strong iodoform odor will be produced, and yellow crystals will form in the tube.

Test for Diacetic Acid.—Fifteen cubic centimetres of urine should be treated with a dilute solution of ferric chloride (not too acid) as long as a precipitate forms. This should be removed by filtration, and the filtrate again treated with the ferric chloride. A claret-red color indicates the presence of diacetic acid. To verify this, a second fifteen cubic centimetres of urine should be boiled and tested in the same manner. This should give a negative result, as the diacetic acid is decomposed by boiling.

Test for B. oxybutyric Acid.—This requires the resources of a well-equipped laboratory. In the presence of acetone and diacetic acid, the presence also of B. oxybutyric acid may be assumed if the polariscope shows a strong rotation to the left of the plane of polarized light, in the absence of levulose and the glycuronates.